Adverse reactions to wine: think outside the bottle

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Purpose of review

Wine contains chemical and biological contaminants. Symptoms such as facial flushing, asthma and oral allergic swelling and burning (oral syndrome) have been attributed to these contaminants and food additives. Their clinical implications should be known.

Recent findings

Recent studies have reported a high prevalence of hypersensitivity symptoms after intake of alcoholic drinks in the general population. Red wine was the most common beverage implicated. Wine contains many contaminants. Some of them come from Hymenoptera insects that fall into the wine when grapes are collected and pressed. We have found patients with allergic symptoms related to wine consumption who are sensitized to Hymenoptera venom without previous stings. The aim of this study is to assess the potential importance of their sensitization to Hymenoptera antigens as the cause of their symptoms and also to comment on other recent studies on wine hypersensitivity.

Summary

We found patients with allergic symptoms related to wine consumption who are sensitized to Hymenoptera venoms. Challenges were negative with sulfites, other additives and aging wines, but positive with young wines. Sera from all the patients detected Hymenoptera venom antigens. We report the first cases of sensitization to venom antigens by the oral route.

Keywords

Hymenoptera venom allergy, sulfite, wine

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Introduction

Wine is the most common beverage implicated in hypersensitivity symptoms after consumption of alcoholic drinks. Here, we review the most recent published studies on this subject.

Epidemiology

Although many persons with allergic symptoms report alcoholic drinks, more precisely wine, as triggers of their symptoms [1••], little is known about the mechanisms of these reactions. Hypersensitivity symptoms after consumption of alcoholic drinks are more common in asthmatic patients [1••,2••], but recent studies report a high prevalence of hypersensitivity symptoms after the intake of alcoholic drinks in the general population. In an adult northern European general population survey, the prevalence of alcohol-induced symptoms involving the upper airways, lower airways or skin was 7.6%, red wine being the most common beverage implicated [1••]. In a study performed by Nilhen and colleagues [3] on 11 933 randomly selected adult individuals, red wine and white wine were the most frequent triggers of alcohol-induced nasal symptoms (83 and 31% of the subjects, respectively).

Chemical contaminants

Wines may have chemical contaminants (sulfites, dioxin, histamines, polychlorides, biphenyls, hexachlorobenzene, polybromide diphenyl ether, aromatic hydrocarbons, naphthalene, arsenic, cadmium, mercury and lead). The sulfite family of food additives has been implicated in the pathogenesis of wine-induced asthma. Nevertheless, a few studies investigating the role of sulfites in wine-induced asthma have yielded equivocal results [2••]. Only a small number of wine-sensitive asthmatic patients responded to a single-dose challenge with wine containing sulfites under laboratory conditions. This may suggest that the role of sulfites in triggering asthmatic responses has been overestimated. Alternatively, cofactors or other components of wine may play an important role in wine-induced asthma. Cumulative sulfite dose challenges did not lead to an increased sensitivity to sulfite in wine-sensitive asthmatic patients, and an alternative approach to identify sulfite/wine-sensitive asthma could be required.

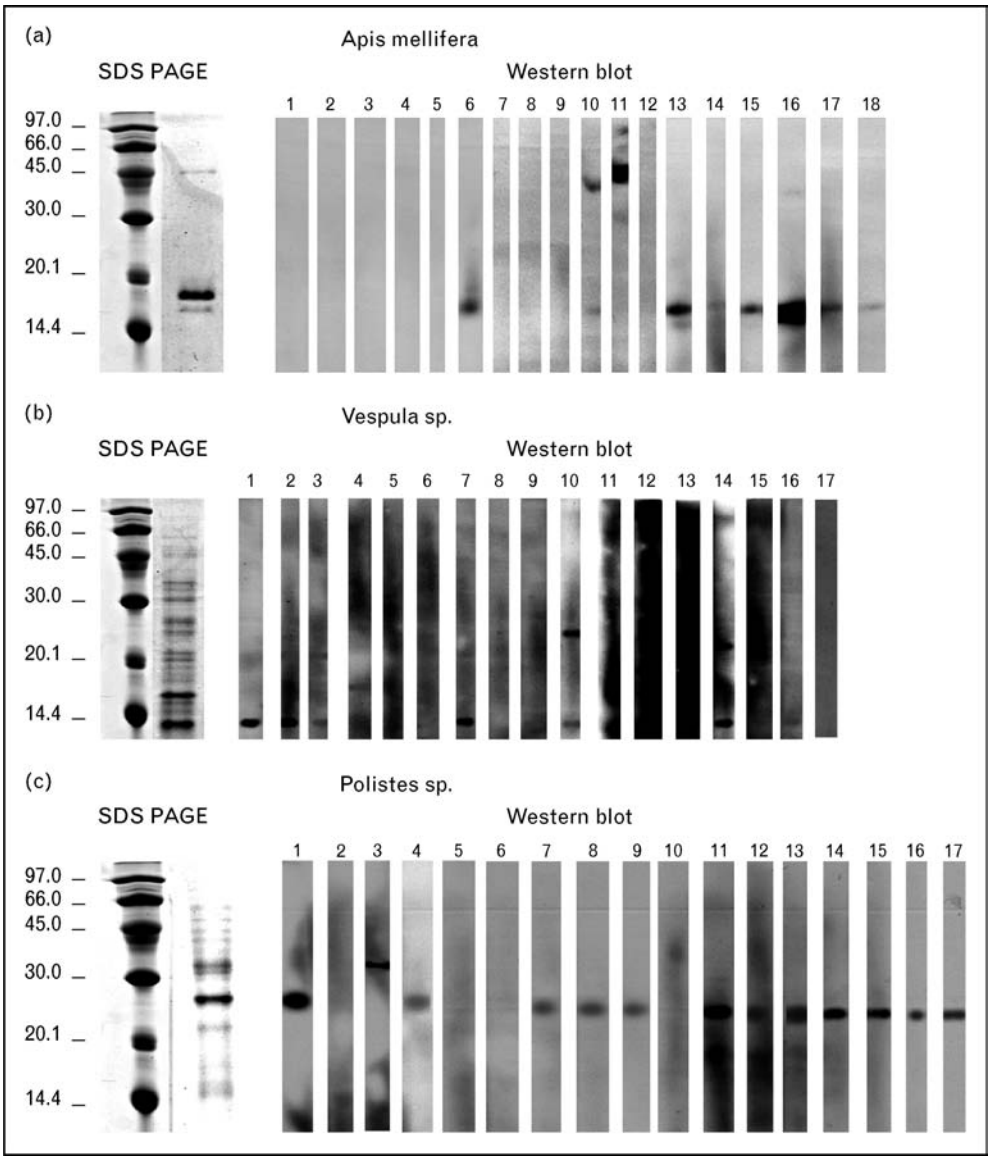
Ethanol has been implicated in skin reactions and in urticarial and anaphylactoid reactions [4]. A possible allergic reaction to acetaldehyde could not

be excluded in these patients. In addition to this, sensitivity to ethanol itself can play a role in triggering adverse responses particularly in Asians, which is due mainly to a reduced capacity to metabolize acetaldehyde. On the contrary, bronchial constriction after wine and other foods rich in histamine may be caused by decreased histamine degradation on the basis of reduced activity of diaminoxidase. Histamine in wine may induce asthma in patients suffering from histamine intolerance.

Wine allergens

Allergy to grape is uncommon; however, allergic reactions to different types of grape and wines have been described, and exercise-induced allergy to grape has also been recently reported [5•,6]. Western blot analysis of grape and red wine extracts revealed specific immunoglobulin E (IgE) reactivity to three allergens in grapes and red wine previously identified as 30-kDa endochitinase 4A and 4B, 24-kDa thaumatin-like protein and

Figure 1 The immunoblotting with patients' sera, wine supplied by our patients and aging wines



(a) Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE) 15% and immunoglobulin E (IgE) immunoblotting to *A. mellifera* extract. Lanes 1–6: patient's sera. Lanes 7–11: positive controls' sera to Hymenoptera venom. Lanes 12–18: positive control sera to *A. mellifera* venom. (b) SDS PAGE 15% and IgE immunoblotting to *Polistes* sp. extract. Lanes 1–6: patient's sera. Lanes 7–11: positive controls' sera to Hymenoptera venom. Lanes 12–17: positive control sera to vespid's venom. (c) SDS PAGE 15% and IgE immunoblotting to *Vespula* sp. extract. Lanes 1–6: patient's sera. Lanes 7–11: positive controls' sera to Hymenoptera venom. Lanes 12–17: positive control sera to vespid's venom.

9-kDa lipid transfer protein. Grape chitinases account for 50% of the soluble proteins of grapes and persist through the process of fermentation of wine.

Wines may also have potentially allergenic food proteins such as casein, milk, egg white and isinglass (fish derived), due to the use of the products as potential clarifying or fining agents. Rolland *et al.* [7] investigated whether wines fined using these proteins or nongrape-derived tannins (tree-nut derived) can provoke significant clinical allergic reactions (anaphylaxis) in patients with confirmed IgE-mediated relevant food allergy. They performed a double-blind placebo-controlled trial using a large panel of Australian commercial wines fined using one or more of the legislation-targeted food proteins. The authors concluded that these foods present an extremely low risk of anaphylaxis in fish, egg or peanut allergic consumers. In fact, it could be assumed that fining agents would be almost completely removed during the manufacturing process; however, until now there has been no necessity to analyze wine for these fining agents. By applying enzyme-linked immunosorbent assay (ELISA), Weber and colleagues [8••] performed measurements of residuals of fining agent proteins and the stabilizer lysozyme in various German wines. Their results showed no detectable amounts of fining agents in wines, except for dried egg white and lysozyme.

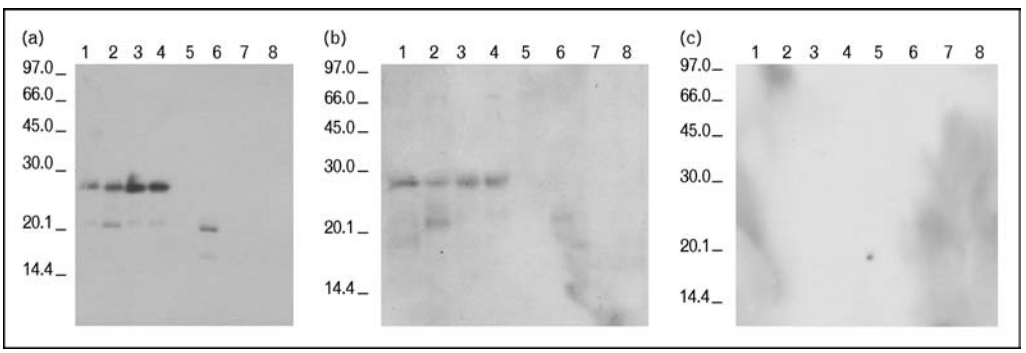
One of the biological pollutants most observed by vineyard workers was insects, specifically, Hymenoptera that fall into the wine when grapes are collected and pressed.

We have recently reported five patients who presented with symptoms after drinking grape juice or newly pressed wines (both red and white) [9]. Three presented with an oral allergy syndrome and facial flushing, one with asthmatic symptoms and one with anaphylaxis. Skin tests with conventional allergens, including commercial grape extract, egg white and wines aged for up to 1 year, were negative. No patient had a history of ingesting drugs containing sulfites concomitant with these symptoms. None had been stung by Hymenoptera species, yet all had positive skin tests and IgE levels (>0.35, CAP, Phadia, Uppsala, Sweden) specific to Hymenoptera (*Apis mellifera*, *Vespula* sp. and *Polistes* sp.) and to the wine under suspicion. We assessed potential sensitization to Hymenoptera antigens as the cause of their symptoms.

Those with symptoms after red wine were sensitive to *Vespula* sp. and *Polistes* sp. (both), whereas those with symptoms after white wine were sensitive only to *Polistes* sp. Patch tests and oral and bronchial challenge tests with sulfites were negative in all five patients. Four had a positive reaction to an oral challenge with the wine they had ingested (OAS and flushing), and the remaining patient (who presented with asthma symptoms) showed a 25% decrease in FEV_1. Challenges with aging wines were negative.

Figure 1 shows the immunoreactivity of the patient's serum samples with extracts of different Hymenoptera venoms. Immunoblots (Fig. 2) revealed two 22-kDa and 27-kDa allergens from grape juice, freshly pressed wines and one aging wine (22 kDa), recognized by reactive patient sera and Hymenoptera positive control patient sera. Aging wines (except for one sample) did not reveal IgE-binding capacity to these allergens. *Polistes* sp. venom extract as the inhibitory phase (immunoblot inhibition), with patients' and Hymenoptera positive control patient sera, inhibited IgE binding to these proteins. Immunoblot inhibition with *Vespula* sp. and *A. mellifera* venom extracts as the inhibitory phase did not show any inhibition (data not shown).

Figure 2 Immunoglobulin E (IgE) immunoblotting to extracts of different wines



Lane 1: red grape first press; lane 2: white grape first press; lane 3: Emilio Moro's wine first press; lane 4: Emilio Moro's wine first press at 4 weeks; lane 5: Ribeiro's aging wine; lane 6: Penedes' aging wine; lane 7: Wine Gran reserva Rioja 1994; lane 8: Mosto GREIP. (a) Patients' pooled sera. (b) Positive controls' Hymenoptera-allergic sera. (c) Positive controls' Hymenoptera-allergic and patients' pooled sera inhibited with *Polistes* sp. venom.

In summary, venom antigens found in the wines were from venoms of the most prevalent Hymenoptera species in Spain. Among vespids, sensitization to *Polistes* sp. is more frequent than sensitization to *Vespula* sp. in our area. These cases of sensitization to Hymenoptera with allergy symptoms after drinking wine indicate that sensitization to Hymenoptera venom can occur through the oral route.

Conclusion

Although hypersensitivity symptoms following alcoholic drink consumption are more common in asthmatic patients, recent studies report a high prevalence of hypersensitivity symptoms following the intake of alcoholic drinks in the general population. Red wine was the most common beverage implicated. Wine contains many additives and biological contaminants. Some of them come from Hymenoptera insects that fall into the wine when grapes are collected and pressed.

In our cases, aging red wines did not produce any response. The possibility of Hymenoptera sensitization seemed to be related to the time of collection of wine, and young wines may contain minimal quantities of venom antigens. After fermentation, the antigen can become denatured as suggested by our results. Advice to those patients that have presented allergic symptoms after drinking wines may be to only drink aging wines.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 283).

1 Linneberg A, Berg N, Gonzalez-Quintela A, Vidal C. Prevalence of self-reported hypersensitivity symptoms following intake of alcoholic drinks. Clin Exp Allergy 2008; 38:145–151.

This study showed the high prevalence of hypersensitivity symptoms following alcoholic drink consumption in an adult general population and the association of these symptoms with the prevalence of allergic rhinitis and asthma.

2 Vally H, Thompson PJ, Misso NL. Changes in bronchial hyperresponsiveness following high- and low-sulphite wine challenges in wine-sensitive asthmatic patients. Clin Exp Allergy 2007; 37:1062–1066.

This study did not support a major role of the sulphite additives in wine-induced asthmatic response in patients studied with a well performed challenge test. They considered that the changes following wine challenge were not consistent with a single cause.

3 Nilhen U, Greif J, Nyber P, *et al.* Alcohol-induced upper airway symptoms: prevalence and co-morbidity. Respir Med 2005; 99:762–769.

4 Nakagawa Y, Sumikawa Y, Nakamura T, *et al.* Urticarial reaction caused by ethanol. Allergol Int 2006; 55:411–414.

5 Alcobeda Borras E, Botey Faraudo E, Gaig Jane P, Bartolome Zabala B. Alcohol-induced anaphylaxis to grape. Allergol Immunopathol 2007; 35:150–161.

The authors report a case of alcohol-induced anaphylaxis to grape. Alcohol was a cofactor of the hypersensitivity.

6 Sbornik M, Rakoski J, Mempel M, *et al.* IgE-mediated type-I-allergy against red wine and grapes. Allergy 2007; 62:1339–1340.

7 Rolland JM, Apostolou E, Deckert K, *et al.* Potential food allergens in wine: double-blind, placebo-controlled trial and basophil activation analysis. Nutrition 2006; 22:882–888.

8 Weber P, Teinhart H, Pasche A. Investigation of the allergenic potential of wines fined with various proteinogenic fining agents by ELISA. J Agric Food Chem 2007; 55:3127–3133.

In this study, residuals of fining agent proteins and the stabilizer lysozyme were investigated in various German wines, which showed no detectable amounts of fining agents except for dried egg white and lysozyme. They concluded that adverse reactions against egg proteins in treated wines could not be excluded.

9 Armentia A, Pineda F, Fernandez S. Wine-induced anaphylaxis and sensitizaton to hymenoptera venom. N Eng J Med 2007; 357:719–720.